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N-Pyridinium imidates as new sources of 2-aminoimidazole and imidazoline derivatives

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ABSTRACT

New 2-aminoimidazole (2-AI) and imidazoline derivatives were obtained in three steps through the reduction of *N*-pyridinium imidates into 1,2-dihydropyridine imidates and oxidative addition of guanidine derivatives. Among the possible transformations, imidate substitution allows selectivity in the last deprotection step, leading to an original 2-aminoimidazolo-imidazoline skeleton.

The 2-aminoimidazole (2-AI) subunit is found in various active marine metabolites isolated from sponges, for example, 3-amino-1-(2-aminoimidazol-4-yl)-prop-1-ene (**1**),[1] girolline (**2**),[2] and oroidin (**3**)[3] (Fig. 1). Due to various biologically interesting activities of imidazole and 2-aminoimidazole heterocycles, many lead molecules have been selected as synthetic targets.[4]

In the synthesis of the oroidin-type alkaloids, the construction of the 2-AI core is commonly envisaged by an addition reaction between acetylguanidine and an α-halocarbonyl,[5] by cyanamide condensation on a 2-aminoaldehyde[6], or by oxidative addition of protected guanidines **7** to 1,2-dihydropyridines **6** followed by dihydropyridine ring opening to give the 2-AI derivatives **9**.[7] This latest approach allows selective access to a large library of *Z*/*E* analogs of the marine natural compound oroidin (**3**). An interesting diversity of the 2-AI core could be simply reached by using various N-substituted-N′-protected guanidines[8,9] (Scheme 1).

For other structural modifications, we have used a second generation of the early dihydropyridine building block prepared from the corresponding pyridinium salt. Following a similar reaction sequence, a modification of the starting material is needed for the replacement of the oroidin pyrrole moiety by other groups, for example, phenyl or alkyl. As reported by Fowler, *N*-acyl-1,2-dihydropyridines are not accessible by simple reduction of the corresponding *N*-acylpyridinium salt.[10] In general, 1,2-dihydropyridines with a free position at C_2 are unstable compounds. To be of practicable use, they have to be stabilized by an *N*-alkoxycarbonyl substituent or by the *N*-acylpyrrole, as we have demonstrated in the synthesis of oroidin and derivatives.[8,9] Inspired by the interesting work of Charrette et al. regarding the use of 2-substituted-1,2-dihydropyridines in the synthesis of piperidine alkaloids,[11] we thought of using *N*-pyridinium imidate salts of type **11** as precursor of the desired 1,2-dihydropyridines. This would allow a large substitution panel on the imidate function as presented by R_1 and R_2 (Scheme 2).

The 1,2-dihydropyridines **12** were synthesized in one pot from pyridine and the appropriate benzamide derivatives **10** (Scheme 3).[12] *N*-Pyridinium imidate salts of type **11** were obtained following the optimized reaction conditions. Subsequent borohydride reduction afforded the (*E*)-1,2-dihydropyridines **12** in 4/1 regioisomeric ratio of 1,2/1,4, respectively. The latter regioselectivity is in accordance with the regioselectivities obtained when reducing the *N*-acylpyrrole pyridinium by the borohydride (Table 1).[8]

2-Aminopyrimidine (2-AP) was selected as a highly protected guanidine. Standard conditions were used for the oxidative addition of the 2-AP to dihydropyridines **12**.[8] This led to the formation of the bicyclic adducts **13** in acceptable yields (Scheme 4).

Deprotection of the guanidine[13] and formation of the 2-AI moiety by dihydropyridine ring opening were performed in one step by treatment with hydroxylamine hydrochloride (3 equiv) and triethylamine (3 equiv) in absolute ethanol. Under these conditions, all the starting material was consumed but the resulting reaction mixture was rather messy. When the amidine function was substituted by a methyl or a benzyl group the major compound was product **17**, which exhibited an original 2-aminoimidazolo-imidazoline

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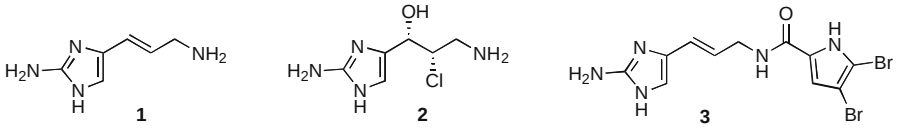
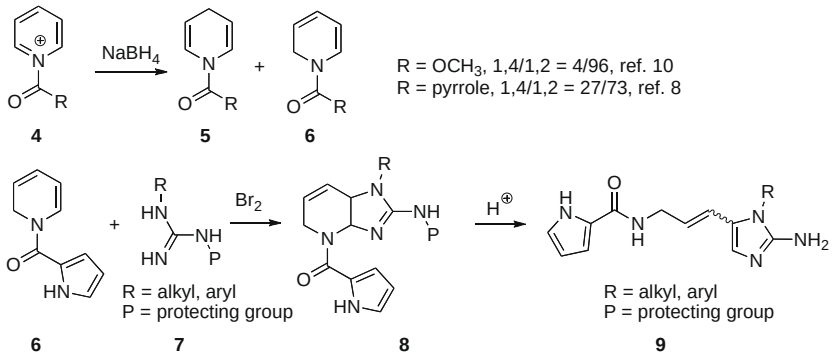
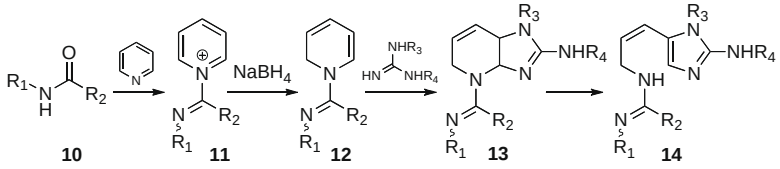


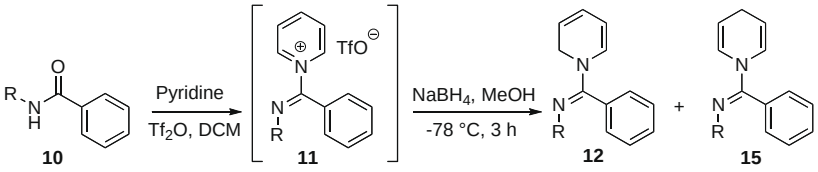
Figure 1.



Scheme 1.



Scheme 2.

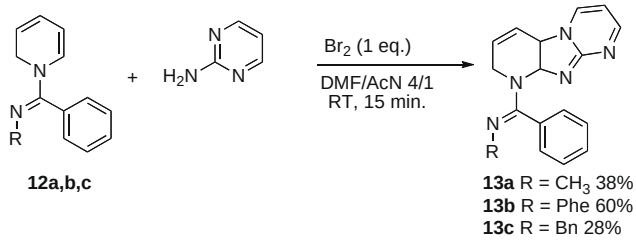


Scheme 3.

Table 1

Entry	Benzamide	R	**12**/**15**[a]	Yield[b] (%)	Product
1	**10a**	CH_3	84/12	67	**12a**
2	**10b**	Phe	73/27	65	**12b**
3	**10c**	Bn	80/20	34	**12c**

[a] Determined by ^{1}H NMR.
[b] **12**+**15**.

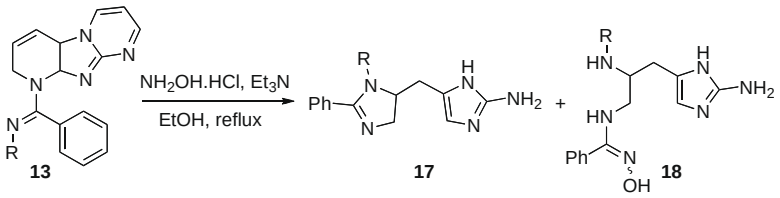


Scheme 4.

skeleton. When the amidine was substituted by a phenyl group, the major product was the 2-aminoimidazole derivative **18b** (Scheme 5 and Table 2).

Deprotection of the guanidine function followed by opening of the dihydropyridine ring afforded transitorily the expected compound **16**[14] which immediately rearranges into compound **17**. Formation of the imidazoline ring was the consequence of the intramolecular addition of the amidine function on the expected tautomer generated by the dual reactivity of the 2-AI nucleus.[7a] A similar rearrangement has already been observed in the last step of pyrrolo-2-aminoimidazole alkaloid synthesis while heating under acidic conditions.[8] Electrophilic reactivity of the amidine carbon of compound **17b** was enhanced by substitution of the N1″ by a phenyl group, leading to the hydroxylamine nucleophilic addition, followed by ring opening to afford **18b** (Scheme 6).[15]

The reaction sequence was extended to the dihydropyridine **20** prepared in one pot from the pyrrolidone (**19**). The dihydropyridine **20** was obtained as described above, in one pot from **19** in 56% yield. Oxidative addition of 2-AP underwent the formation of the bicyclic adduct **22** in 38% yield. Interestingly, deprotection of the guanidine and concomitant ring opening afforded three



Scheme 5.

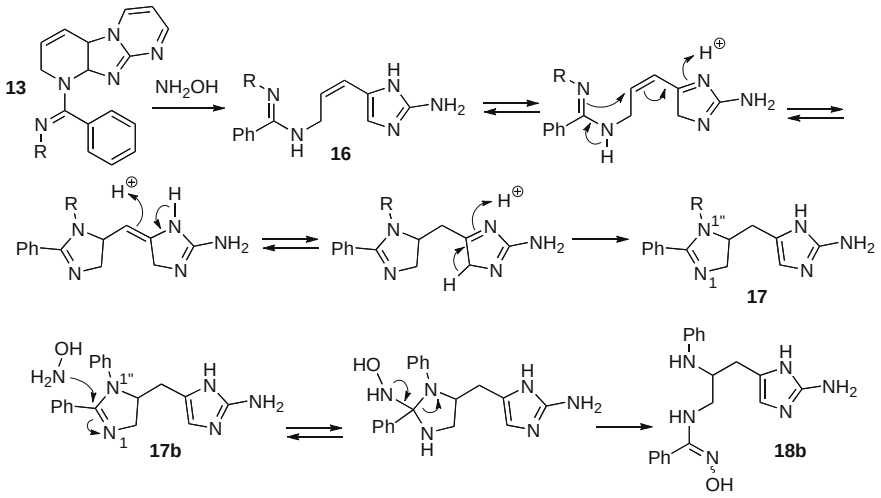
Table 2

Entry	Substrate	R	*t* (h)	**17**[a] (%)	**18**[a] (%)
1	**13a**	CH_3	3	**17a** (41)	–
2	**13b**	Phe	1	**17b** (6)	**18b** (48)
3	**13c**	Bn	1	**17c** (33)	

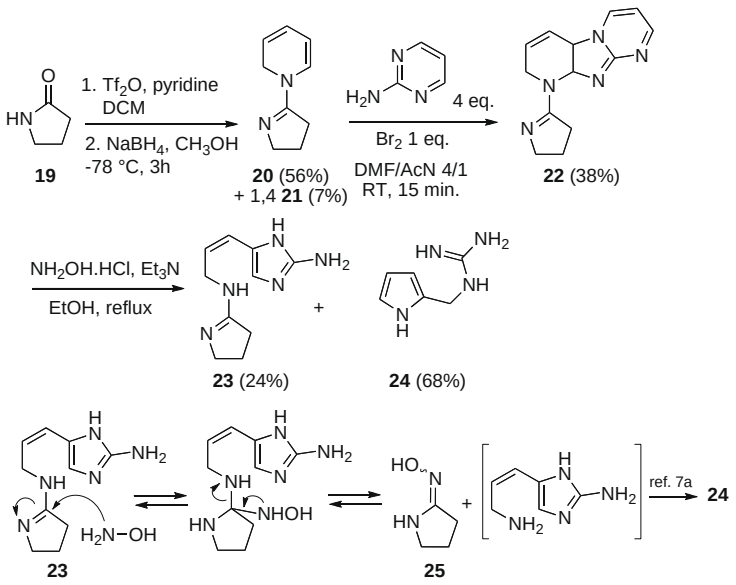
[a] Isolated yield.

different compounds. Next to the expected product **23** isolated in 24% yield, the major compound **24** was obtained in 68% yield (Scheme 7). The known product **24**[7a] resulted from the cleavage of the amidinic bond by the hydroxylamine, departure of the pyrrolidin-2-one oxime (**25**), followed by spontaneous intramolecular cyclization of the unstable allylic amine on the 2-aminoimidazole moiety.

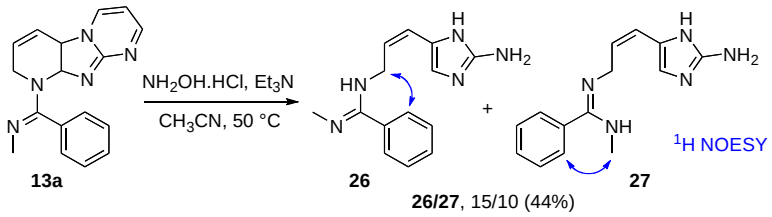
Finally, in order to limit the rearrangement process, further examination of the experimental conditions was conducted on compound **13a**. Under optimized conditions, treatment of the bicyclic adduct **13a** by hydroxylamine hydrochloride (2 equiv) and triethylamine (2 equiv) in acetonitrile at 50 °C gave the expected



Scheme 6.



Scheme 7.



Scheme 8.

product in a reasonable yield of 44%, as two inseparable tautomers **26** and **27** as the sole identifiable products (Scheme 8).

In conclusion, new 2-aminoimidazole and imidazoline derivatives were obtained in three steps from *N*-pyridinium imidates. Imidate substitution by a methyl or a benzyl group allowed selective formation of original 2-aminoimidazolo-imidazoline compounds, while substitution by a phenyl group or a cyclic imidate function underwent the formation of open interesting rearranged derivatives. Applications of these selective trends are in progress and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.101.

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